RECURRENT APHTHOUS STOMATITIS - IN SOME PATIENTS VITAMIN B12 COULD BE A “MASTER KEY”

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ABSTRACT Introduction: Idiopathic recurrent oral aphthosis or recurrent aphthous stomatitis (RAS) is a benign disease of the oral cavity that affects a significant portion of the population. Despite numerous studies, its etiology often remains unknown, and there is no ideal therapeutic approach. The differential diagnosis is vast. Case Report: We present a 16-year-old female with complaints of multiple oral thrushes with two months of evolution, unresponsive to usual topical treatments. She presented macrocytosis (maximum VGM 133 fl), vitamin B12 levels within reference values and folic acid levels at the limit of normality. With other negative investigations, having opted for vitamin B12 supplementation with complete resolution of her complaints. Our objective was to confirm the beneficial treatment of RAS with vitamin B12 supplementation. Conclusion: Treatment with vitamin B12 is simple, inexpensive and low risk and seems to be effective for a large percentage of patients suffering from RAS, regardless of serum vitamin B12 level.

KEYWORDS Cyanocobalamin, Macrocytosis, Pediatric age, Recurrent aphthous stomatitis, Vitamin B12

Introduction

Oral aphthosis is an ulcerated lesion that appears in the oral cavity. Typically, they are painful, superficial, well-circumscribed, round or oval, fibrin-covered, greyish-yellow lesions with a hyperemic border. The most commonly affect the non-keratinized mucosa (labial and jugal mucosa, soft palate, ventral surface of the tongue and floor of the mouth), but can appear anywhere in the oral cavity, including the keratinized mucosa (hard palate and gums) and on the specialized mucosa of the dorsal surface of the tongue. When this lesion presents as recurrent episodes in the absence of a systemic cause, it is called Idiopathic recurrent oral aphthosis or recurrent aphthous stomatitis (RAS) and is a common reason for referral. They affect up to 25-30% of the general population, and recurrence rates at 3 months are as high as 50%.[1,2]

RAS can be classified into three types, minor, major and herpetiform. Minor aphthous lesions are the most common presentation (80%), measure between 3 and 10 mm in greatest diameter and usually appear on the non-keratinized mucosa (labial and jugal mucosa), ventral face and lateral edges of the tongue. They appear as small, round, clearly defined, painful ulcers that heal in 7 to 14 days without leaving a scar. Major lesions measure 1 to 3 cm in diameter, and the sites most often involved are the keratinized and non-keratinized mucous membranes, especially the soft palate, lips, oropharynx, and tonsils. They usually take 2 to 6 weeks to resolve, and may leave a scar. The third type, herpetiform ulcers, has a female predilection and a typical onset in adulthood. It is characterized by a larger number of oral lesions 1-3 mm in diameter, which may converge into larger irregular ulcerations. They resolve in 7 to 10 days, may or may not leave scars, and recurrences are more frequent.[3]

Although the clinical features of RAS are well defined, the precise etiopathogenesis remains unknown, and it is likely that in genetically predisposed individuals, and immune dysfunction associated with triggering factors facilitates its appearance. Trauma, mineral and vitamin deficits (iron, folic acid/vitamin B9 and cobalamin/vitamin B12), emotional stress, hormonal factors...
and immunodeficiency are described as risk factors. Systemic diseases such as HIV infection, celiac disease, inflammatory bowel disease, Behçet’s disease, Reiter’s syndrome and PFAPA syndrome (Periodic Fever, Aphthae, Pharyngitis and cervical Adenitis) can manifest themselves in this way. However, they represent less than 1% of the causes of RAS. There are also several drugs implicated in oral aphthosis, including non-steroidal anti-inflammatory drugs, anticonvulsants and immunosuppressants. There is no consensus on its association with allergy or intolerance to specific foods.[1,4,5]

Generally, there is no effective treatment for RAS when the specific underlying cause is not known, resorting to palliative treatments such as administration of local anaesthetics, anti-inflammatory drugs including topical and systemic corticosteroids, or surgical methods. To treat recurrence, it is important that the therapeutic approach is not only symptomatic. To this end, it is essential to establish a complete diagnosis whenever possible.[6,7]

In the literature, there are few studies and with insufficient numbers of patients with RAS reporting significant cure rates by cyanocobalamin supplementation in case of cobalamin/vitamin B12 deficiency.[5,8,9,10] Putting our hypothesis that there is the efficacy of cyanocobalamin treatment in patients with RAS who have normal or low serum cobalamin levels, we describe the case of a young patient with RAS. Their vitamin B12 replacement therapy led to her complete recovery.

**Case report**

A 16-year-old female with no previous pathological history had come to our department complaining of RAS of about two months’ evolution, with painful lesions on the labial mucosa and tongue, without significant improvement with topical treatment (trimacinolone and hyaluronic acid). She had a varied and balanced diet, no dietary restrictions, no known triggering or infectious events, no gastrointestinal or musculoskeletal symptoms, and no systemic symptoms such as fever, night sweats, or weight loss. There was no family history of autoimmune disease. Objective examination showed countless (more than 20) minor lesions on the tongue border and labial mucosa, with no other changes, including genital aphtha, no skin lesions, no alopecia and no Raynaud’s phenomenon. Patergy’s sign was negative.

The pediatrician assistant had already performed laboratory tests, revealing macrocytic anemia (Hb 11 g/dL, VGM 133 fL). Additional laboratory tests revealed a serum level of vitamin B12 (362 pg/mL - reference values 211-911 pg/mL) and folic acid (5 ng/mL - reference values > 5.4 ng/mL).

Trial therapy was given with vitamin B12 (10mg/2mL IM, 2 administrations) and folic acid (5 mg id) with complete resolution of the thrush after four weeks. In the meantime, in a multidisciplinary approach, the adolescent was also seen at a haematology consultation, where she underwent a study directed at macrocytosis and gastroenterology to continue with the etiological investigation of vitamin B12 deficit. In addition to a low/borderline folic acid value and vitamin B12 levels within reference values, she had a peripheral blood smear with macrocytosis and neutrophils with aberrant nuclear segmentation and reticulocytes of 57x10⁶/L. She had elevated fetal haemoglobin (HbF) values (high-performance liquid chromatography with AFA2 profile: HbA 2.6% and HbF 5.9%) and a possible sideropenia was also assumed (ferritin of 30 ng/mL with a sedimentation rate (SV) of 31 mm/1h). A diepoxynbutane (DEB)-induced chromosomal instability test was negative (Fanconi anaemia, a cause of myelodysplasia, was ruled out). Thyroid function and liver enzymes were unchanged. Anti-intrinsic factor (IF) and anti-gastric parietal cell antibodies were negative, and celiac disease was excluded. Faecal calprotectin was negative, and upper digestive endoscopy, colonoscopy with biopsies, and magnetic resonance enterography identified no changes.

He was given daily iron and folic acid supplementation and intramuscular vitamin B12 monthly (20 months) and later at 2/2 month and 4/4-month intervals. Currently, after 5 years of follow-up in the haematology department, he is taking vitamin B12 every 3/3 months, with no other new complaints, with recurrence of thrush only when there was occasional non-compliance with the medication.

**Discussion**

There are several possible causes of RAS. The macrocytosis, however, led to suspicion of cobalamin deficit.

Macrocytic anemias may be megaloblastic (vitamin B12 or folic acid deficit) or non-megaloblastic. A mild macrocytosis, VCM 100-110 fl, with or without anaemia, often occurs in the course of liver disease, inadequate alcohol intake, hypothyroidism, hemolysis, aplasia, bone marrow infiltration or dysplasia.[11]

Macrocytosis due to cobalamin or folic acid deficiency is the direct result of ineffective or dysplastic erythropoiesis. These vitamins are the necessary and most important cofactors for the normal maturation of all cells, and cobalamin is necessary for DNA synthesis, as its deficit prevents cell division in the marrow.[11,12] When there is a deficit of either of these cofactors, the red blood cells become large, erythroblasts with nuclear or cytoplasmic asynchrony (poikilocytosis), a characteristic of all megaloblastic anaemias.[11,13] Megaloblastic anaemia occurs when cobalamin stores fall below 0.1 mg.[14] During early childhood, the HbF level decreases to less than 1% of total haemoglobin. However, in a number of acquired and inherited diseases, increased HbF levels are found in adulthood. Acquired increases in HbF are virtually all restricted to conditions involving disturbances in erythropoiesis. HbF, as a marker of marrow stress, is increased in these cases of vitamin B12 and folic acid deficiency, as well as in myelodysplasias.[15,16] Anemia and macrocytosis are factors that influence increased sedimentation velocity (SV).[17]

The existence of a correlation between RAS and serum cobalamin levels has been the subject of several recent studies.[4,5,18,19] The association between cobalamin deficit and RAS may be explained by the role of cobalamin in DNA synthesis, as previously mentioned. Cell-mediated immunity is suppressed, and changes occur in the tongue epithelium and oral mucosa. These changes are analogous to those seen in the blood and bone marrow in cases of insufficient DNA synthesis.

Vitamin B9 (folic acid) is also involved in the formation of coenzymes for protein synthesis and erythropoiesis. It has recently been shown that oral mucosal changes, including glossitis and stomatitis, may be the only clinical signs of early vitamin B12 or folic acid deficiency.[20]

The results of a double-blind placebo-controlled study indicate that vitamin B12 treatment was associated with decreased pain level, number of oral ulcers, and duration of flare-ups in patients with RAS. These results did not depend on the initial vitamin B12 level.[21] Indeed, although many research studies and clinical laboratories define vitamin B12 deficiency at a level below 150 pg/mL, or in some cases 200-250 pg/mL, patients...
with values above these values may be symptomatic and benefit from vitamin supplementation, as was the case described.[22] For this reason, vitamin B12 levels below 500 pg/mL are valued in our hospital, depending on the clinic.

To increase the specificity and sensitivity when diagnosing vitamin B12 deficiency, the concept of investigating the levels of homocysteine (HCY), methylmalonic acid (MMA) and holo-transcobalamin II (holoTC) has aroused great interest in some studies. However, diagnostic algorithms that dose vitamin B12, MMA and HCY are reflected in some studies and their negative predictive values have not been established. Thus, identifying and dosing of “functional” vitamin B12 deficit remains controversial.[23] This entity was not excluded in our case, and MMA, HCY or holoTC were not dosed. However, it should be noted that the probability of “functional” vitamin B12 deficit decreases when the vitamin B12 level increases in the blood. Since the vitamin B12 level in our patient was greater than 250 pg/mL, the probability of “functional” vitamin B12 deficit was low. Another explanation for the possible effects of vitamin B12 in treating RAS is that it is assumed that vitamin B12 must have other functions that are not yet fully known.[24] Genetic mutations and insufficient nutritional intake are the main causes of vitamin B12 deficiency in the pediatric age. Cobalamin is present only in foods of animal origin and is absorbed in the last part of the small intestine (ileum). However, to be absorbed, this vitamin must be combined with FI in the duodenum, the protein produced by gastric parietal cells. Without this, vitamin B12 remains in the intestine and is excreted in the faeces. Therefore, most cobalamin is stored in the liver.[25] In the case presented, the adolescent had an unrestricted diet and investigation for causes of intestinal malabsorption was negative, and no reason was found for the deficit presented.

Conclusion

With the clinical case presented, the authors intend to alert that supplementation with vitamin B12 and folic acid seems to be an effective treatment for patients with RAS, regardless of the serum level of vitamin B12. Thus, and especially in the case of macrocytosis, it is important to raise the diagnosis of vitamin B12 deficiency. Furthermore, the treatment is simple and inexpensive and has no known significant adverse effects; therefore, in these cases, the authors propose a therapeutic trial with cobalamin, as performed in the adolescent of the presented case, where a complete and effective resolution of the RAS was achieved.

What this case report adds?

- Deficiencies of vitamin B12 and folic acid are rare in the pediatric age.
- If a patient has recurrent oral thrush or recurrent aphthous stomatitis, it is important to check HCM values and vitamin B12 and folic acid levels and consider treatment with vitamin supplementation.
- HbF is a marker of spinal cord stress and is increased in vitamin B12 and folic acid deficits. In addition, it is also increased in spinal cord failure syndromes, so its dosage is mandatory.
- Treatment with cyanocobalamin may be beneficial for patients with RAS, even when serum cobalamin levels are normal. For mucosal protection, prevention of recurrence and treatment of lesions, higher serum cobalamin levels (500 pg/mL) should be achieved in patients with RAS.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

References


